IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Jef DE BRABANDER, et al.

Title: ***SYNTHESIS OF PELORUSIDE A AND ANALOGS THEREOF FOR USE AS ANTITUMOR AGENTS***

Appl. No.: 10/783,848 Filing Date: 2/20/2004

Examiner: A. Owens Art Unit: 1625

DECLARATION UNDER 37 CFR § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

I, Jef De Brabander, hereby declare that:

1. I am a Full Professor in the Department of Biochemistry at The University of Texas Southwestern Medical Center at Dallas, for the Board of Regents, The University of Texas System, which is the assignee of the captioned application.

2. I conduct research in the fields of chemical synthesis and biological evaluation of biologically active compounds. My qualifications are set out in my *curriculum vitae*, which is attached hereto as APPENDIX A.

3. I am named as an inventor in the captioned application. I also have read and believe that I have understood an office action, dated September 12, 2007, which concerns the application, and certain supporting documents cited in the action, namely, J. Jiménez-Barbera *et al. J. Am. Chem. Soc.* 128 (2006) 8757-8765 ("Jiménez-Barbera"); O. Pineda *et al. Bioorg. Med. Chem. Lett.* 14 (2004) 4825-4829 ("Pineda"); X. Liao *et al. Angew. Chem. Int. Ed.* 42 (2003) 1648 ("Liao"); Y. C. Martin *et al. J. Med. Chem.* 45 (2002) 4350-4358; and F. Z. Dörwald, *Side Reactions in Organic Synthesis*, p. ix (2005, Wiley-VCH Verlag GmBH & Co. KGaA, Weinheim).

4. The Examiner rejected claim 6 on the grounds that the claimed peloruside A spiroacetal analogs are neither (1) synthetic intermediates to peloruside A nor (2) therapeutically active like peloruside A and, hence, the compounds lack utility. I understand the Examiner to rationalize these conclusions primarily by citation to Jiménez-Barbera and Pineda for the proposition that the recited spiroacetal moieties will distort the macrocycle conformation, such conformation being critical to microtubule binding.

5. The spiroacetal analogs recited in claim 6 are not intended to be synthetic intermediates to peloruside A. These compounds are instead therapeutically active compounds in their own right.

6. Computational and experimental data show that the spiroacetal compounds recited in claim 6 feature the same macrocyclic conformation as in peloruside A. Specifically, Appendix B depicts the three-dimensional structure of peloruside A as determined by NMR studies. Notably, the 'top' of the molecule features two hydroxyl groups on carbon atoms 9 and 11, respectively, that lie on the same side of macrocycle. Exhibit B shows these hydroxyl groups as 'pointing' up from the plane of the paper. Although not shown explicitly in the Exhibit, the orientation of the hydroxyl groups engenders hydrogen bonding between the groups, *i.e.*, O-H···O, giving rise to a constrained macrocycle by virtue of a ring comprised of carbon atoms 9, 10, 11, the two oxygen atoms, and the hydrogen-bonded hydrogen atom.

7. Drawing upon the NMR studies mentioned above, Appendix C illustrates in two representations the computational structure of peloruside A. Peripheral substituents and hydrogen atoms are omitted to clearly depict the conformation of the macrocycle.

8. Finally, Appendix D illustrates two representations of the (2-naphthyl)methylidene acetal at carbon atoms 9 and 11 that is featured in the Liao publication cited by the Examiner. Computational and NMR studies generated these representations, which depict only the key acetal moiety in order to emphasize the conformation of the macrocycle in this region.

9. A comparison of the structures in Exhibits B, C, and D reveals that the presence of the spiroacetal moiety at carbon atoms 9 and 11 does not change the conformation of the macrocycle, relative to that in peloruside A itself. This result is rationalized from the observation that the spiroacetal moiety is an isostructural replacement of the hydrogen-bonded hydroxyl groups at C-9 and C-11 in peloruside A. Thus, in contrast to the Examiner's stated beliefs, the spiroacetal derivatives of claim 6 do not manifest a "drastic change in the conformational sense," but instead they preserve the macrocycle conformation that is critical to tubulin-binding activity. That is to say, the cyclic acetal locks the macrocycle into an active conformation.

10. I understand the Examiner separately to reject claims 4-12 and 23 for lack of enablement, based primarily upon three synthetic challenges relating to the claimed compounds. First, the Examiner would doubt the availability of two cyclopropyl starting materials, respectively designated as "A" and "B" in the Office Action, that are necessary to synthesize the claimed cyclopropyl derivatives. Second, the Examiner draws attention to synthetic intermediate 61F in Figure 90 of the application, supposing that the olefinic bond in 61F will be dihydroxylated and then cleaved, thereby preventing the synthesis of claimed compounds

lacking substituents $-OR^4$ and $-OR^6$. Finally, the Examiner doubts the ability of a skilled chemist to make the claimed compounds that feature the full scope of substituents at position R^8, reasoning that the presence of R^8 results from aldol reactions that have not been performed.

11. First, the replacement of *gem*-dimethyl substituents with a cyclopropyl group is generally a straightforward modification falling well within the capabilities of an organic chemist. To illustrate this principle in the context of macrocycle synthesis, I enclose a review article on macrocycles known as epothilones (K.C. Nicolau *et al. Angew. Chem. Int. Ed.* 37 (1998) 2014-2045). On page 2037, Scheme 38 details the construction of various epothilone libraries that interchangeably employ *gem*-dimethyl and cyclopropyl building blocks designated as compounds **31** and **236**, respectively. That is to say, exactly the same chemistry operates on **31** and **236**, thereby demonstrating the ease with which cyclopropyl analogs are made.

The synthetic challenge in making the claimed cyclopropyl compounds is no greater. For instance, cyclopropyl ketone "A" is known as its parent alcohol **Ia** in T. S. Kuznetsova *J. Org. Chem. USSR* 28 (1992) 256-262 (copy enclosed). A detailed synthesis of **Ia** is set forth on page 259 of the publication. Benzyl protection of this primary alcohol to give compound "A" is a basic organic transformation well within the grasp of the synthetic chemist ("Protective Groups in Organic Synthesis" by Theodora W. Greene, Peter G. M. Wuts 3rd Edition, June 1999; **ISBN:** 0-471-16019-9; John Wiley & Sons Inc).

Further, cyclopropyl ketone "B", which features a trimethylsilyl ether, is known as its *tert*-butyldimethylsilyl ether (**32**) in K.C. Nicolau *et al. Chem. Eur. J.* 3 (1997) 1957-1970 (copy enclosed). Compound **32** is depicted in Scheme 5 on page 1960, and its synthesis is described on page 1966. As any expert in the field of organic synthesis would recognize, a variety of known silylether protecting groups are interchangeable, such as *tert*-butyldimethylsilyl and trimethylsilyl (Green and Wuts (1999)).

12. Second, basic synthetic principles controvert the Examiner's challenge to the viability of intermediate compound 62F in Figure 90. Precursor compound 61F in Figure 90 undergoes transformation in steps s-v to compound 62F *via* formation of an intermediate olefinic compound that is not shown in the scheme. The success of the reaction sequence to produce 62F turns, in part, upon the fact that the intermediate olefin is terminal and electron-rich, which position the olefin ideally for the necessary dihydroxylation and subsequent cleavage steps. In contrast, the olefinic bond in question at the 'bottom' of 61F and bearing the $-CO_2Me$ substituent is internal and electron-poor, rendering this bond unreactive under the conditions prescribed for making 62F (for a representative review, see: H.C. Kolb, M.S. VanNieuwenhze and K.B. Sharpless, *Chem. Rev.* **94** (1994), pp. 2483–2547).

13. Third, the aldol reaction that installs substituent R^8 in the claimed compounds requires only modest attention by those who are skilled in organic synthesis. This textbook reaction prescribes, for instance, the deprotonation of a methyl ketone $R^8C(O)CH_3$ with a suitable base to give the corresponding enolate $R^8C(O)CH_2^-$. The enolate subsequently reacts with the aldehyde moieties in compounds 62A-J that are recited in claim 24. Nothing about this reaction would strike the skilled chemist as remarkable, much less "far from straightforward and highly unpredictable" as characterized in the Office Action; indeed, the very fact that the aldol reaction is so widely employed, and the substrates so great in number, is not a synthetic obstacle, but rather testament to a rich and accessible diversity at R^8.

Modification of the macrocycle peripheral substituents, such as R^8, presents a far less synthetic challenge than changes to the macrocycle itself. Moreover, given the discussion above, variations at R^8 would not exert as much influence upon the activity of the compounds as would conformational changes to the macrocycle. Thus, the compounds should tolerate a substantial variation in structure at R^8 from synthetic and therapeutic perspectives.

14. Finally, I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issuing thereon.

Respectfully submitted,

Date 02-12-2008 By _____

Jef De Brabander